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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,351	06/07/2002	Stace Lindsay	06727/008002	8638

21559 7590 04/02/2010

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
04/02/2010	ELECTRONIC

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte STACE LINDSAY,
ROBERT MULROY, and DANIEL SEMENTUK

Appeal 2009-012966
Application 10/030,351
Technology Center 1600

Decided: March 31, 2010

Before TONI R. SCHEINER, LORA M. GREEN, and
MELANIE L. McCOLLUM, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the rejection of claims 1, 6, 7, and 21-27, directed to recombinant human alpha-fetoprotein (rHuAFP) operably linked to a milk-specific promoter, and a non-human transgenic animal that expresses rHuAFP. The claims have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

Claims 1, 6, 7, and 21-27 are pending and on appeal, and stand rejected under 35 U.S.C. § 103(a) as unpatentable over DeBoer,[1] Clark,[2] Lubon,[3] Morinaga,[4] and Bennett.[5]

Claim 1 is representative of the subject matter on appeal:

1. A substantially pure nucleic acid molecule comprising: (i) a nucleic acid sequence encoding recombinant human alpha-fetoprotein (rHuAFP), (ii) a milk-specific promoter, said promoter being operably linked to said rHuAFP-encoding sequence, and (iii) a leader sequence encoding a protein secretory signal that enables secretion of said rHuAFP by milk-producing cells into the milk of a mammal.

ISSUE

The issue raised by this appeal is whether the Examiner has established that it would have been obvious to express recombinant human alpha-fetoprotein in the milk of a transgenic mammal.

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[1] US Patent 5,633,076, issued May 27, 1997 to DeBoer et al.
[2] US Patent 5,322,775, issued June 21, 1994 to Clark et al.
[3] US Patent 5,831,141, issued November 3, 1998 to Lubon et al.
[4] Tomonoki Morinaga et al., *Primary structures of human α-fetoprotein and its mRNA*, 80 PNAS 4604-4608 (1983).
[5] James A. Bennett et al., *Similarity between natural and recombinant human alpha-fetoprotein as inhibitors of estrogen-dependent breast cancer growth*, 45 BREAST CANCER RESEARCH AND TREATMENT 169-179 (1997).

FINDINGS OF FACT

DeBoer, Clark, Lubon, Morinaga, and Bennett

FF1 The Examiner made a number of factual findings with respect to the DeBoer, Clark, Lubon, Morinaga, and Bennett references (Ans. 4-5), which we adopt as our own.

Essentially, the DeBoer, Clark, and Lubon references disclose non-human transgenic mammals with genomes comprising transgenes encoding various human proteins - including serum albumin, lactoferrin, lysozyme, Factor IX, and Protein C - operatively linked to milk-specific promoters, and to leader sequences encoding protein secretion signals, so that the transgenic products are secreted into the milk of the mammals.

FF2 In addition, as acknowledged by Appellants (App. Br. 8), these references suggest expressing many other recombinant proteins in the mammary gland, but none specifically suggests expressing human alpha-fetoprotein this way.

FF3 Morinaga discloses the sequence of human alpha-fetoprotein, while Bennett discloses functional rHuAFP made in *E. coli*.

Appellants' Evidence on Rebuttal

FF4 The fatty acid content of cow, goat, and human milk is shown in Table 3 from "Compositions of Foods; Dairy and Egg Products"; Agricultural Handbook No. 8-1, published by the Agricultural Research Service, Washington, DC; USDA (1976); submitted as Appellants' Exhibit A with the Reply to Office Action filed October 31, 2007. Table 3 is reproduced below:

TABLE 3. COMPARISON OF COW, GOAT, AND HUMAN MILK/100 gms

FATTY ACID (gm)	COW	GOAT	HUMAN
Saturated			
Total	2.80	2.67	2.01
C4:0	.11	.13	—
C6:0	.06	.09	—
C8:0	.04	.10	—
C10:0	.08	.26	.06
C12:0	.09	.12	.26
C14:0	.34	.32	.32
C16:0	.88	.91	.92
C18:0	.40	.44	.39
Monounsaturated			
Total	.96	1.11	1.66
C16:1	.08	.08	.13
C18:1	.84	.98	1.48
C20:1	trace	—	.04
C22:1	trace	—	trace
Polyunsaturated			
Total	.12	.15	.59
C18:2	.08	.11	.37
C18:3	.05	.04	.05
C18:4	trace	—	—
C20:4	trace	—	.03
C20:5	trace	—	trace
C22:5	trace	—	trace
C22:6	trace	—	trace

Source:
Adapted from "Composition of Foods; Dairy and Egg Products", Agricultural Handbook No. 8-1, Agricultural Research Service, Washington, D.C.; USDA, 1976.

Table 3 shows the fatty acid content of milk from cows, goats, and humans.

FF5 Vallette[6] teaches that "[m]ammalian α-feto-proteins (AFPs) are oncofetal antigens which exhibit a complex molecular heterogeneity involving differences in size, charge, carbohydrate moiety and ligand contents (fatty acids and estrogens)" (Vallette 302, col. 1). Vallette teaches that saturated fatty acids have no effect on the binding and immunological properties of rodent and human AFPs (*id.*, Abstract), but "an unsaturated fatty acid environment induces conformational changes in AFP which may modulate the endocrine and immune functions of this protein" (*id.*), although the effects are transitory (*id.* at 311, col. 2).

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[6] Geneviève Vallette et al., *Conformational changes in rodent and human α-fetoprotein: influence of fatty acids*, 997 BIOCHIMICA ET BIOPHYSICA ACTA 302-312 (1989).

FF6 Haourigui[7] teaches that, in vitro and in vivo, "unsaturated FFA [free fatty acids] induce conformational changes in rat AFP" (Haourigui 164, col. 2), and "[o]ne of the most striking findings is the reversible effect of the rise of FFA on the binding and immunological properties of AFP, indicating that AFP could adapt to, and interact with the environmental changes which occur during ontogenesis, oncogenesis and in pathological situations" (*id.*).

FF7 Parmelee[8] describes a "relatively mild procedure for purifying α-fetoprotein from fetal tissue. The protein prepared by this method has been found to contain a variety of fatty acids . . . The fatty acids can be removed from the protein by using procedures analogous to those employed to remove fatty acids from albumin" (Parmelee 2114, col. 2). According to Parmelee, the α-fetoprotein "can be reconstituted with fatty acids to yield material with properties similar to the original preparation" (*id.*).

PRINCIPLES OF LAW

The Supreme Court has emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). "Often, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in

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[7] M. Haourigui et al., *In vivo transient rise in plasma free fatty acids alters the functional properties of α-fetoprotein*, 1125 BIOCHIMICA ET BIOPHYSICA ACTA 157-165 (1992).

[8] David C. Parmelee et al., *The Presence of Fatty Acids in Human α-Fetoprotein*, 253 J. BIOL. CHEM. 2114-2119 (1978).

the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed" (*id.* at 418-19). To paraphrase *KSR*, if a technique has been used to improve one process or product, and a person of ordinary skill in the art would recognize that it would improve similar processes or products in the same way, using the technique is obvious unless its actual application is beyond his or her skill (*id.* at 417).

"If a *prima facie* case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed." *In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986).

> A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.

In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

ANALYSIS

The Examiner acknowledges that "[n]either DeBoer, Clark nor Lubon taught human AFP as the protein being expressed in the mammary glands of the mammals" (Ans. 5). Nevertheless, the Examiner concluded that:

> [I]t would have been obvious . . . to make the claimed transgenic mammals and milk derived therefrom as taught by each of DeBoer, Clark and Lubon wherein the gene expressed and secreted into the milk was the rHuAFP gene as taught by

> Morinaga. It would have been obvious to replace the various genes of each of DeBoer, Clark and Lubon with the rHuAFP gene, as expression of a transgene in the mammary gland was an art accepted means of producing large quantities of recombinant protein. One of ordinary skill in the art would have been sufficiently motivated to produce large quantities of rHuAFP for use in cancer therapy as Bennett taught that recombinant human AFP can effectively bind estrogen and may be a regulator of estrogen-dependent human breast cancer.

(*Id.* at 5-6.)

Appellants contend that the Examiner "has articulated a new rule, not found in the M.P.E.P. or any other authority: no one can be granted a patent on the expression of any protein in the milk of a transgenic mammal, regardless of what the art teaches about that protein, and regardless of the results obtained by the inventors" (App. Br. 7). Appellants contend that this "unfairly and improperly places the burden on Appellants to overcome what is in effect a ready-made *prima facie* case of obviousness, without the Office actually having to make the case" (*id.*).

Nevertheless, Appellants do not dispute any of the Examiner's fact findings regarding the DeBoer, Clark, Lubon, Morinaga, and Bennett references. Nor have Appellants identified any flaw in the Examiner's rationale for combining the references, except for asserting that the Examiner's rejection "is classic impermissible hindsight" (*id.*).

We disagree. The Examiner established that "the availability of large quantities of homogeneous, biologically active recombinant human AFP" would be desirable to one of ordinary skill in the art, and that "expression of a transgene in the mammary gland was an art accepted means of producing large quantities of recombinant protein" (Ans. 5). We agree with the

Examiner that the cited references would have given one of skill in the art a reason, and the means, to generate a non-human transgenic animal capable of expressing rHuAFP in milk.

Appellants contend that "[e]ven if [the references relied on by the Examiner] could be read to direct the skilled artisan to express rHuAFP in the milk of a transgenic mammal" (App. Br. 10), "publications available prior to Appellant's filing date direct the skilled artisan away from the expression of rHuAFP in milk" (*id.*), and the evidence of record "provides no reasonable expectation that the expression of biologically active rHuAFP in milk would be successful" (*id.* at 16).

Relying on Table 3 from "Compositions of Foods; Dairy and Egg Products," Appellants contend that "milk is known to contain an abundant amount of free fatty acids (FFAs), including mono-and poly-unsaturated acids" (App. Br. 10). Appellants contend that "[o]ne of skill in the art would not know, *a priori*, whether expression of rHuAFP in the milk of a transgenic mammal would yield a rHuAFP having the desired biological activity" (*id.* at 13), and:

> [G]iven the time and expense required to produce a transgenic mammal, one skilled in the art, having knowledge of, e.g., Vallette et al., Haourigui et al., and Parmelee et al., all of which teach that HuAFP, when exposed to an environment rich in FFAs, will bind to FFAs that induce changes in the conformation and biological activity of HuAFP, would not seek to produce biologically active rHuAFP in the milk of a transgenic mammal.

(*Id.* at 11.)

We are not persuaded by Appellants' evidence or arguments. First, Appellants have not explained how the various amounts and/or types of

unsaturated fatty acids, and the conditions used in Vallette, Haourigui, and Parmelee compare with the amounts of unsaturated fatty acids and conditions in milk. Moreover, the references cited by Appellants indicate that the biological properties of α-fetoprotein are modulated by unsaturated fatty acids, but they also teach that these properties are readily reversible, and that fatty acids ran be removed from (or added to) the protein by conventional processes (FF5-FF7).

Having reweighed all the evidence of record, we are not persuaded that Vallette, Haourigui, and Parmalee would have discouraged one of skill in the art from expressing human alpha-fetoprotein in mammary gland, or that one of skill in the art wouldn't have had a reasonable expectation that the invention would succeed.

CONCLUSIONS OF LAW

The Examiner has established that it would have been obvious to express recombinant human alpha-fetoprotein in the milk of a transgenic mammal.

The rejection of claims 1, 6, 7, and 21-27 under 35 U.S.C. § 103(a) as unpatentable over DeBoer, Clark, Lubon, Morinaga, and Bennett is affirmed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110